Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

N-Phenyl-*N*′-pyridylureas: stereochemical basis for anticonvulsant activity

Arthur Camerman,[a]† Andrew Hempel,[b] Donald Mastropaolo[a] and Norman Camerman[a,b]*

[a]Ardono Research, 341 101st Avenue SE, Bellevue, WA 98004, USA, and [b]Department of Biochemistry, University of Toronto, Medical Sciences Building, Toronto, Canada M5S 1A8
Correspondence e-mail: norman.camerman@utoronto.ca

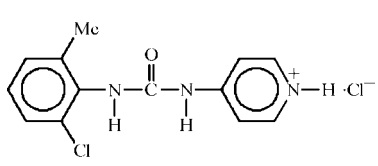
Received 16 January 2006
Accepted 15 February 2006
Online 11 March 2006

4-[*N*-(2-Chloro-6-methylphenyl)ureido]pyridinium chloride, $C_{13}H_{13}ClN_3O^+\cdot Cl^-$ (CI-953 hydrochloride), crystallizes with $Z' = 2$ in $P\overline{1}$. In both molecules, the methyl groups and Cl atoms on the benzene rings are disordered. The benzene rings of molecules *A* and *B* adopt two conformations, differing by a rotation of 180° about the C—N bond to the ureido group, in an approximate 1:1 ratio. This disorder is further enhanced by the rotation of the methyl groups in both adopted positions. The pyridine and benzene rings intersect at angles of 102.1 (1) and 111.3 (1)° for *A* and *B*, respectively. Hydrogen bonding is mediated by Cl^- anions, resulting in indirect connectivity between the molecules. Superposition of the molecular structure, after 180° rotation about an amide bond, with that of phenytoin shows that the chemically different molecules possess stereochemical features in common, which may explain their common activities.

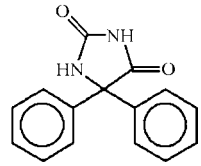
Comment

N-Phenyl-*N*′-pyridinylureas were shown (Lobbestael *et al.*, 1986) to possess anticonvulsant activity in the NIH–NINCDS Antiepileptic Drug Discovery Program. Subsequently, synthesis and testing of a series of over 50 substituted derivatives (Pavia *et al.*, 1990) led to identification of *N*-(2-chloro-6-methylphenyl)-*N*′-4-pyridylurea (CI-953) as having the most desirable *in vivo* profile for a potential anticonvulsant drug. The overall pharmaceutical effects of CI-953 in animal models were similar qualitatively and quantitatively to those of the well known antiepileptic drug phenytoin. These pharmacological similarities led us to determine the crystal and conformational structures of CI-953 in order to ascertain if it possessed stereochemical features in common with the chemically different drug phenytoin, which might be responsible for their similar anticonvulsant properties.

CI-953 hydrochloride, (I), crystallizes with $Z' = 2$ (Fig. 1). The two independent molecules have similar conformations, with approximately planar pyridinylurea fragments intersecting the 2,6-disubstituted phenyl ring planes at angles of 69 and 78°. The phenyl rings in both molecules exist in two possible conformations differing by a 180° rotation about the



(I)



phenytoin

C3—N8 bond, resulting in positional disorder of the *ortho* Cl atoms and methyl groups, with each occupying 50% of each position in the crystal structure. This disorder is further augmented by rotational disorder of the methyl H atoms in both positions. Protonation occurs at pyridine atom N15 in both independent molecules. As shown in Fig. 1, the two CI-953 molecules are indirectly linked through hydrogen bonds (Table 1) from the two urea imine groups in each to a chloride anion, a strong intermolecular interaction made possible by/resulting in the *cis* conformation of the imine H atoms (Fig. 2). In addition, a C—H···O hydrogen bond links the type *A* molecules (Table 1). Van der Waals interactions also contribute to the crystal packing. Intramolecular bond distances and angles are consistent with normal values.

Stereochemical features common to several chemically different types of anticonvulsant drugs, and which are likely determinants of their antiepileptic activity, have been established (Camerman & Camerman, 1980). They consist of two electronegative atoms (hydrogen-bond acceptors), approximately 4.5–5.5 Å apart, and at least one hydrophobic group (benzene ring or equivalent) at a particular location and orientation relative to those atoms. These findings are further supported by a recent study (Thenmozhiyal *et al.*, 2004) of the anticonvulsant properties of a series of phenylmethylenehydantoins, which found that the most important structure–

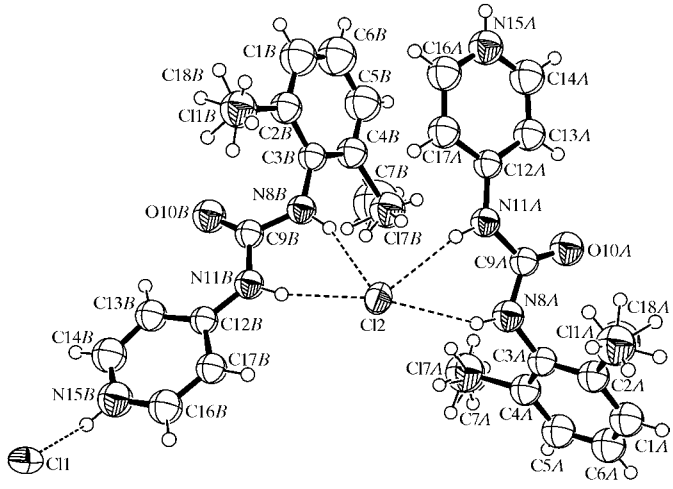


Figure 1
The molecular structure of (I), showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

  DOI: 10.1107/S0108270106005543

activity descriptor, in essence, was the molecular electronegativity or electron-donor capabilities. Although CI-953 is chemically very different from the other drugs studied, we have investigated through molecular superpositions whether similar stereochemical features could exist in CI-953.

Superpositions of CI-953 with phenytoin (Camerman & Camerman, 1971), the best known and conformationally most rigid of the anticonvulsants, were carried out by maximizing the fit of the two most electronegative atoms, *viz*. carbonyl atom O10 and pyridine atom N15, with the carbonyl O atoms of phenytoin. These superpositions did not result in a fit of the substituted phenyl group of CI-953 with a phenyl ring of phenytoin, even if allowable phenyl-ring rotations were invoked. However, as noted above, the observed CI-953 molecular conformation has *cis* imine H atoms, a conformation favored because of intermolecular hydrogen bonding to the chloride ions. In the absence of this crystallographically imposed feature, a molecular conformation featuring a *trans* relation of the urea imine H atoms would also be plausible. Accordingly, we produced that conformation by a rotation of 180° about the N8—C9 bond. We then superposed this CI-953 structure with phenytoin by a least-squares maximization of the fit of three atoms in each molecule, *viz*. atoms O10 and N15 in CI-953 with the carbonyl O atoms in phenytoin, and an aromatic C atom in each (C5 in CI-953 and C11 in phenytoin). The results are shown stereoscopically in Fig. 3. Despite the differences in chemical structure, the two electronegative atoms in each molecule occupy similar positions in space, and the disubstituted phenyl ring of CI-953 has a similar position and orientation to a phenyl ring of phenytoin. Since these features are the mediators of anticonvulsant activity in phenytoin, the stereochemical results presented here are persuasive evidence that these features are responsible for the similar anticonvulsant effects of CI-953, and that the two drugs probably involve very similar mechanisms.

It is also noteworthy that in the series of *N*-phenyl-*N*′-pyridylureas synthesized and tested for anticonvulsant activity the most promising analogs, in addition to CI-953, were the 2,6-dimethylphenyl and 2,6-dichlorophenyl compounds. This suggest that the primary function of these groups is to ensure, through steric interactions, that the benzene plane is roughly perpendicular to the plane of the rest of the molecule, thus maintaining an orientation similar to that of a phenyl ring in phenytoin. The small size of the substituents is also necessary to limit the overall size of the hydrophobic entity in this position.

The efficacy of many antiepileptic drugs is attributed to interactions with ion channels or neurotransmitter systems (Malawska, 2005), but their therapeutic mechanisms at the molecular level are not well understood. Although broad classification of drugs into categories based on a particular mechanistic system is possible, this has limited value because most anticonvulsants possess more than one mechanism of action. The identification of common stereochemical features in chemically different anticonvulsant molecules facilitates new drug design independent of the mechanism(s) of action.

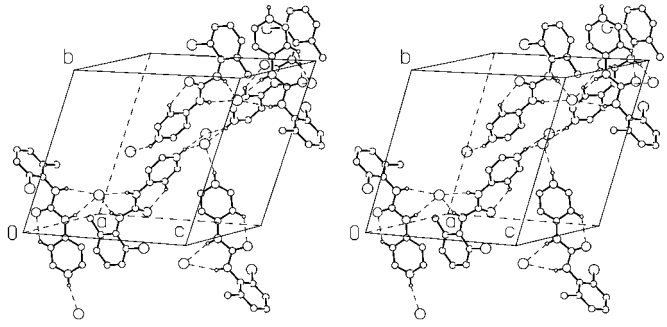


Figure 2
A stereodiagram of the molecular packing and hydrogen-bond scheme. Atoms are drawn as circles of arbitrary radii. For clarity, only the H atoms participating in hydrogen bonding are shown.

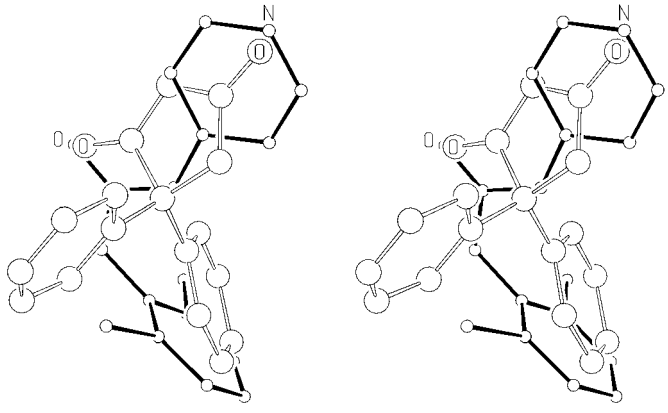


Figure 3
A stereodiagram of the superposition of rotated CI-953 (filled bonds, small circles) and phenytoin. Electronegative atoms are labeled (O is oxygen and N is nitrogen).

Experimental

Crystals suitable for data collection were obtained by dissolving CI-953 in methanol and subsequently subjecting the solution to slow evaporation. Small crystals grew in about three weeks. Attempts to grow better crystals in order to avoid disorder proved unsuccessful.

Crystal data

$C_{13}H_{13}ClN_3O^+\cdot Cl^-$
M_r = 298.16
Triclinic, $P\overline{1}$
a = 8.022 (3) Å
b = 13.193 (4) Å
c = 14.893 (4) Å
α = 69.06 (3)°
β = 81.29 (2)°
γ = 80.60 (3)°
V = 1444.9 (9) Å^3
Z = 4
D_x = 1.371 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 19–45°
μ = 4.01 mm^{-1}
T = 294 (2) K
Needle, colorless
0.52 × 0.12 × 0.08 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.586, T_{max} = 0.724
4418 measured reflections
4272 independent reflections
3375 reflections with $I > 2\sigma(I)$
R_{int} = 0.005
θ_{max} = 60.0°
$h = -4 \rightarrow 9$
$k = -14 \rightarrow 14$
$l = -16 \rightarrow 16$
3 standard reflections
every 100 reflections
intensity decay: 2.7%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0837P)^2 + 0.3467P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.043$	$(\Delta/\sigma)_{max} = 0.003$
$wR(F^2) = 0.134$	$\Delta\rho_{max} = 0.27$ e Å^{-3}
$S = 0.94$	$\Delta\rho_{min} = -0.15$ e Å^{-3}
4272 reflections	Extinction correction: *SHELXL97*
385 parameters	Extinction coefficient: 0.0062 (6)
H-atom parameters constrained	

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N8A—H8A···Cl2	0.86	2.48	3.273 (3)	154
N8B—H8B···Cl2	0.86	2.37	3.183 (3)	158
N11A—H11A···Cl2	0.86	2.34	3.173 (3)	163
N11B—H11B···Cl2	0.86	2.30	3.131 (3)	164
N15A—H15A···Cl1^{i}	0.86	2.26	3.072 (3)	158
N15B—H15B···Cl1	0.86	2.53	3.155 (3)	131
N15B—H15B···Cl1^{ii}	0.86	2.82	3.397 (3)	126
C13A—H13A···O10A	0.93	2.27	2.864 (4)	121
C13A—H13A···O10A^{iii}	0.93	2.48	3.186 (4)	133
C13B—H13B···O10B	0.93	2.26	2.850 (4)	121

Symmetry codes: (i) $-x+1, -y, -z+1$; (ii) $-x+2, -y+1, -z+1$; (iii) $-x, -y, -z$.

All H atoms, except those of the methyl groups, were initially located in a difference map and were well behaved during refinement; however, a low data-to-parameter ratio justified placement of the H atoms in calculated positions in a riding-model approximation. An overall isotropic displacement parameter was refined for all H atoms except for the methyl groups. The final U_{iso}(H) value was 0.08 (3) Å^2 and the distances were 0.86 (N—H) and 0.93 Å (C—H). H atoms of methyl groups were refined as idealized disordered groups with two positions rotated from each other by 60°, and the methyl C atoms and the Cl atoms were refined with partial occupancies set to sum to unity. The C—H distances were fixed at 1.0 Å.

Data collection: *Picker Operating Manual* (Picker, 1967); cell refinement: *Picker Operating Manual*; data reduction: *DATRDN* (Stewart, 1976); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1429). Services for accessing these data are described at the back of the journal.

References

Camerman, A. & Camerman, N. (1971). *Acta Cryst.* B**27**, 2205–2211.

Camerman, A. & Camerman, N. (1980). *Antiepileptic Drugs: Mechanism of Action*, edited by G. H. Glaser, J. K. Penry & D. M. Woodbury, pp. 223–231. New York: Raven Press.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Lobbestael, S. J., Nordin, I. C. & Fleming, R. (1986). US Patent No. 4 6297 31; *Chem. Abstr.* **103**, P71195Y.

Malawska, B. (2005). *Curr. Top. Med. Chem.* **5**, 69–85.

North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

Pavia, M. R., Lobbestael, S. J., Taylor, C. P., Hershenson, F. M. & Miskell, D. L. (1990). *J. Med. Chem.* **33**, 854–861.

Picker (1967). *Picker Operating Manual.* Picker, Cleveland, Ohio, USA.

Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97.* University of Göttingen, Germany.

Stewart, J. M. (1976). *DATRDN: The X-ray System*. Technical Report TR-446 of the Computer Science Center, University of Maryland, College Park, Maryland, USA.

Thenmozhiyal, J. C., Wong, P. T. H. & Chui, W. K. (2004). *J. Med. Chem.* **47**, 1527–1535.